REMARKS

Initially, Applicants would like to thank the Examiner for granting a telephone interview on February 11, 2004, regarding this application. Applicants have attached hereto a copy of a letter sent to the Examiner on February 10, 2004 ("Exhibit A"), which serves as a partial interview summary. During the interview, the Examiner acknowledged that Applicants had presented strong arguments. She further asked Applicants to file this response and present amended claims. Applicants have amended claims 1, 6, 11, and 16 merely to promote clarity. Support for the amendments can be found at page 2, paragraph 2. No new matter has been introduced. **The amendments should be entered as they raise no new issues that will require further consideration or search and also do not touch the merits of the application within the meaning of 37 C.F.R. § 1.116(b).**

Claims 1-20 are pending. Reconsideration of this application is requested in view of the following remarks:

Rejection under 35 U.S.C. § 103(a)

The Examiner rejected all pending claims for obviousness over U.S. Patent 5,470,970 to Sager et al. ("Sager") in view of Ding et al., Proc. Amer. Assoc. Cancer Res., 1996 Vol. 39, page 90 ("Ding"); Rheinwald et al., Cancer Research, 1981, Vol. 41, pp. 1657-1663; Pemberton et al., J. Histochemistry & Cytochemistry, 1997, Vol. 45, pp 1697-1706; the abstracts of Petrovich et al., Radiology 144(4): 905-908, 1982; Weber et al., Otolaryngology – Head and Neck Surgery 99(1): 16-23, 1988; Tytor et al., (Clinical Otolaryngology 15(3): 235-252, 1990; Eiband et al., American Journal of Surgery 158(4): 314-317, 1989; Huwer et al., European Journal of Cardio-Thoracic Surgery 6(9): 498-502, 1992; Nagel et al., Zentralblatt fur Chirurgie 119(4): 225-232, 1994; and van der Velden et al., Cancer 75(12): 2885-2890, 1995.

Applicants respectfully disagree and will first discuss claims 1 and 11, two of the four independent claims. Claim 1 covers a method of determining a relative probability of survival for a subject with squamous cell carcinoma. Claim 11 is drawn to a method of determining whether a subject with squamous cell carcinoma has a lymph node containing cancerous cells.

Both methods include (1) determining a level of maspin gene expression in a biological sample from a subject with squamous cell carcinoma; and (2) comparing the level with a threshold level of maspin gene expression. If the level of maspin gene expression in the biological sample is above the threshold level, it indicates that the subject has a relatively high probability of survival or is free of a lymph node containing cancerous cells.

In the response filed on October 3, 2003, Applicants pointed out that Sager (1) teaches a method based on the discovery that the maspin level decreases during progression to breast cancer, and (2) does not teach that the maspin level decreases during progression to squamous cell carcinoma. None of the secondary references mentions the down-regulation of the maspin level during squamous cell carcinoma development. To the contrary, Ding states that the maspin level increases during progression to squamous cell carcinoma and thereby teaches away from applying the Sager discovery to squamous cell carcinoma.

Nonetheless, the Examiner countered that "Sager provides general teachings ... that the determination of whether or not a cell or tissue is cancerous or metastatic based on decreasing or absent levels of Maspin can be applied to any cell which normally expresses the Maspin gene[,including squamous cell carcinoma]" (emphasis added). See the Office Action, page 6, lines 11-17.

Applicants would like to point out that it is well known in the art that a gene expressed in different types of cells may not be expressed in the same manner during development of cancers derived from them. As pointed out in Applicants' previous response filed on April 3, 2003, maspin is down-regulated in breast and prostate carcinomas but up-regulated in pancreatic and ovarian carcinomas. For example, Sood et al. ("Sood") teaches that over-expression of maspin in ovarian carcinomas is indicative of high tumor grade and short survival. See Exhibit B attached to that response. Sood further refers to Maass et al., which teaches that maspin is over-expressed in pancreatic cancers. Further, according to Ding relied on by the Examiner, "maspin was [also] commonly over-expressed in squamous cell carcinomas," i.e., the level of maspin expression increases during progression to squamous cell carcinoma. In other words, Ding would teach a skilled person from applying Sager's teaching on breast cancer to squamous cell

carcinoma. Indeed, one skilled in the art would recognize that Sanger's "general" teaching is not reliable: while it can be applied to breast and prostate carcinomas, it cannot be applied to ovarian carcinomas, pancreatic cancers, and squamous cell carcinoma.

Here, Applicants note that "[t]he test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts." (Emphasis added). See MPEP 2143.01. Thus, it is improper to consider only Sager and disregard Ding, Sood, and Maass.

For the reasons set forth above, claims 1 and 11 are non-obvious over all the cited references. By the same token, claims 6 and 16, the other two independent claims, are also non-obvious. So are claims 2-5, 7-10, 12-15, and 17-20, all of which depend from claims 1, 6, 11, and 16.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejected all pending claims for indefiniteness, contending that the phrase "threshold level" recited in claims 1-2, 4, 6, 7, 9, 11-12, 14, 16-17, and 19 is not defined. See the Office Action, page 2, lines 5-10.

In the response filed on October 3, 2003, Applicants pointed out that (1) the term at issue is defined based on actual survival curves of a group of patients according to the assay described at page 2, paragraph 2 of the specification; and (2) the pre-determined levels of survival of the patients are used to determine corresponding threshold levels. However, the Examiner maintained the rejection and countered that (1) "the [claim] do[es] not incorporate the survival curve;" and (2) "the pre-determined levels of survival can be ... any value." See the Office Action, page 3, lines 2-6.

Applicants disagree and will discuss independent claims 1, 6, 11, and 16 first.

Note that "[i]t is the function of the descriptive portion of the specification and not that of the claims to set forth operable proportions ... and that claims are not rendered indefinite by the absence of the recitation of such limitations." Ex parte Jackson, 217 USPQ 804 (POBA

1982). As a survival curve is just an operable proportion for the method of claims 1 and 11, these two claims are not rendered indefinite by the absence of its recitation.

Further, contrary to the Examiner's assertion, the pre-determined levels of survival cannot be any value. According to the specification, they are the levels "at which greater than 70% ... of patients survive for at least 50 months (see page 2, paragraph 2)." In other words, the survival level at which 70% of patients survive for 50 months is the lower limit of the pre-determined levels of survival, and the corresponding maspin level is the lower limit of the threshold values.

To determine a relative probability of survival for a test subject with squamous cell carcinomas, one measures the maspin levels of a group of patients and corresponding survival levels to obtain a survival curve. He or she then measures a test subject's maspin level and compares it to the survival curve thus obtained. If that subject's maspin level is above that at which 70% of patients survive for 50 months, the subject is prognozed to have a relatively high probability of survival or to be free of a lymph node containing cancerous cells.

Thus, Applicants submit that the term at issue is clearly defined, and claims 1 and 11 are definite. So are claims 2-5 and 12-15, all of which depend from claims 1 and 11.

Applicants now discuss independent claims 6 and 16. These claims cover methods identical to those covered by claims 1 and 11, respectively, except that if the level of maspin gene expression in the biological sample is below the threshold level, it indicates that the subject has a relatively low probability of survival and a lymph node containing cancerous cells. Thus, contrary to the Examiner's assertions, (1) these claims are not rendered indefinite by not reciting "a survival curve" as a survival curve is just an operable proportion for the claimed methods; and (2) the pre-determined levels of survival cannot be any value, as the level at which 70% of patients survive for 50 months is the upper limit. Therefore, claims 6 and 16 are also definite. So are the claims depending from them, i.e., claims 7-10 and 17-20.

For the purpose of moving this case toward allowance, Applicants have amended claims 1, 6, 11, and 16 to recite the threshold levels.

In view of the above amendments and remarks, Applicants submit that the rejection has been overcome and should be withdrawn.

CONCLUSION

Applicants submit that grounds for the rejections asserted by the Examiner have been overcome, and that claims, as pending, define subject matter that is definite and non-obvious. On this basis, it is submitted that allowance of this application is proper, and early favorable action is solicited.

Please apply any other charges to deposit account 06-1050.

Respectfully submitted,

Date: 3-02-04

Y. Rocky Tsao
Attorney for Applicants
Reg. No. 34,053

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906
20804951.doc